

Cs comprise said gene, and wherein said gene is transmittable through normal sexual reproduction of the transgenic maize plant to subsequent generation plants.

REMARKS

I. Claims in the Case

Claims 2, 3, 4, 47, 56, 57 and 61 have been amended, and claims 1, 5-46 have been canceled without prejudice. Claims 2-4 and 47-67 are currently pending in this case.

II. Petition to Amend Inventorship

In light of cancellation of claims 1 and 5-46, it is necessary for Applicants' to amend the inventorship to reflect the appropriate inventors of the claims that remain. Accordingly, Applicants enclose petition under 36 C.F.R. § 1.48(b)(1), along with the appropriate fee, to amend the inventorship to comport with the amendments to the claims. In particular, of the original listed inventors, the following individuals are no longer listed as inventors:

Thomas R. Adams, Sheryl A. Chambers, Paul S. Chomet, Richard J. Daines, Kimberly Glassman, Lucille B. Laccett, Peggy G. Lemaux, Mary Lou Mangano, Michael T. Mann, James V. O'Brien, Thomas B. Rice, T. Michael Spencer, William G. Start, Clayton S. Vetsch, Nancy G. Willetts, Susan J. Zachwieja

Thus, the following individuals are the inventors of the presently pending claims:

Paul C. Anderson, Christopher E. Flick, William J. Gordon-Kamm, Albert P. Kausch, Catherine J. Mackey, Emil M. Orozco, Peter Orr, Michael A. Stephens, David A. Walters, Donald S. Walters

Additionally, it is noted that the present case was filed as a CIP of USSN 07/565,844, which is still pending. While Applicants are not necessarily relying on the filing date of the '844 case for the claims that remain pending in the present case, Applicants desire to maintain a reference to the earlier-filed application to allow for the possibility of later filings under section 120.

III. Rejection of Claims 2-4 Under 35 U.S.C. § 101

First, the Action rejects claims 2-4 under 35 U.S.C. § 101, taking the position that these claims are directed to non-patentable subject matter. The Action states that it is not clear whether these claims are intended to read only upon transgenic plants, in that there is no limitation *per se* in the claim in this regard.

In response, Applicants have amended claims 2-4 in a manner to require that the subject matter of the claim include within its scope the introduced transgene. It is believed that this amendment appropriately addresses the Examiner's concerns. However, the Examiner is encouraged to suggest other language if such would be appropriate.

IV. Provisional Rejection of Claims 44-46 Under 35 U.S.C. § 101

Next, the Action provisionally rejects claims 44-46 as claiming the same invention as that of claims 33-35 of copending application Serial No. 07/636,089.

In response, although claims 44-46 are no longer pending in this case, thus rendering the rejection moot, it is respectfully pointed out that these claims were directed to "hybrid" transgenic plants and therefore not directed to the "same invention" as that of the copending case.

V. Provisional Rejection of Claims 1-67 Under Obviousness-type Double Patenting

Next, the Action rejects all the pending claims as unpatentable over claims 28-68 of copending application Serial No. 07/508,045. The Examiner takes the position that the '045 case is directed to fertile transgenic maize plants that are said to be patentably indistinct from the subject matter of the claims of the present invention.

It is respectfully submitted that the subject matter of claims 47-67 is distinct from the subject matter of the parent application. Claims 47-67 are directed to transgenic maize bearing particular genes that are submitted to be novel and nonobvious in the context of fertile, transgenic corn plants. There is submitted to be no art that teaches, suggests or in any way motivates one of skill in the art to produce the particular transgenic corn plants of claims 47-67. Most notably, there is no motivation for one of skill to produce the specific subject matter of claims 47-67. The Action fails to base its finding upon a teaching, suggestion or motivation to employ each of the claimed genes -- a prerequisite to a finding of obviousness-type double

patenting. *Carmen Industries, Inc. v. Wahl*, 220 U.S.P.Q. 481, 487 (Fed. Cir. 1983); *Mirafi Inc. v. Murphy*, 14 U.S.P.Q. 1337, 1347 (N.C. 1989). To maintain the rejection it must be shown that the subject matter of the later claims is obvious over that of the earlier case, based upon prior art that existed as of the date of invention of the first patent. It is submitted that no such demonstration has been made here.

VI. Rejection of Claims 11, 14, 15, 29, 47, 60 and 63-67 Under 35 U.S.C. § 112, Second Paragraph

Next, the Action rejects 11, 14, 15, 29, 47, 60 and 63-67 Under 35 U.S.C. § 112, second paragraph, with the Action taking the position that these claims are set forth using improper Markush group terminology.

In response, it is respectfully pointed out that MPEP § 706.03(y) specifically provides for the format employed by Applicants. The Examiner's attention is directed to the page 700-22 of the MPEP, col. 2, lines 15-18, which states that:

... "wherein R is a material selected from the group consisting of ABC and D" is a proper limitation, then "wherein R is ABC or D" shall also be considered proper.

Here, Applicants' claims follow the latter, accepted, format. Accordingly, it is respectfully submitted that the structure of the rejected claims is appropriate.

VII. Rejection of Claim 43 Under U.S.C. § 112, Second Paragraph

Next, it is believed that the rejection of claim 43 under U.S.C. § 112, second paragraph, is moot in light of the cancellation of this claim without prejudice.

**VIII. Rejection of Claims 47 and 57 Under
35 U.S.C. § 112, Second Paragraph**

Next, the Action rejects claims 47 and 57, taking the position that the phrase "not normally expressed" is both vague and indefinite.

In response, Applicants have amended the claims to remove the complained-of language.

**IX. Objection to the Specification Under
35 U.S.C. § 112, First Paragraph**

The Action next objects to the specification under 35 U.S.C. § 112, first paragraph, but does not reject any of the claims. The Action appears to take the position that while transgenic maize plants bearing certain genes have been properly exemplified, transgenic maize bearing other genes have not. The Action appears to take the position that the specification itself must actually demonstrate expression of the genes in order to meet the "written description" requirement.

Applicants would first respond to the rejection by noting that the written description requirement is in no way relevant to the situation at hand. It is accepted patent law that a "written description" rejection can arise in only one of three situations, none of which are applicable here:

Satisfaction of the description requirement insures that subject matter presented in the form of a claim subsequent to the filing date of the application was sufficiently disclosed at the time of filing so that the *prima facie* date of invention can fairly be held to be the filing date of the application. This concept applies whether the case factually arises out of an assertion of entitlement to the filing date of a previously filed application under § 120 . . . or arises in the interference context wherein the issue is support for a count in the specification of one or more of the parties . . . or arises in an *ex parte* case involving a single

application, but where the claim at issue was filed subsequent to the filing of the application . . . Where the claim is an original claim, the underlying concept of insuring disclosure as of the filing date is satisfied, and the description requirement has likewise been held to be satisfied. (emphasis supplied)

In re Smith, 178 U.S.P.Q. 620, 623-24 (CCPA 1973). Thus, an original claim can never be subject to a written description rejection.

Similarly, in *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1173 (U.S. Int'l Trade Comm. 1983), *aff'd sub nom. Massachusetts Institute of Technology v. AB Fortia*, 227 U.S.P.Q 428 (Fed. Cir. 1985), the Court reiterated that a written description concern can arise only in the context of newly added claims, in that original claims constitute their own written description:

Original claims constitute their own description. Thus, the requirement is important only when the claims have been amended during prosecution of the application at the Patent and Trademark Office (PTO), being a requirement that the new definition of the invention in an amended claim be based on a description originally in the specification. The requirement assures that the newly defined invention is entitled to the original filing date of the application.

Thus, the CCPA and Federal Circuit recognize that a "written description" rejection cannot arise where the claim is an original claim, and one is relying on the filing date of the current application. Claims 47-67 are original to this application, and, for the purposes of this rejection, Applicants are not relying upon the filing date of any earlier application for claims 47-67. Thus, according to legal precedent and the MPEP, there can be no written description concern with respect to claims 47-67.

Turning now to a consideration of possible enablement concerns, the Action states only that absent an actual demonstration of expression, the specification is not in compliance with § 112, first paragraph. It is apparently agreed that the

specification enables the "nuts and bolts" of introducing the claimed genes into corn. Yet, the Action adheres to the erroneous proposition that enablement requires a working example for each gene claimed. Here, the specification admittedly exemplifies the expression of Gus, bar, lux, hyg, aroA and Bt. Moreover, Table 9 of the specification discloses that working progeny have been obtained from GUS, bar, hyg, aroA, Bt and 10kD zein transformed plants. Thus, there is no evidence presented by the Examiner to suggest that the presently recited genes would not express or otherwise function in corn.

Even in unpredictable arts, rejections on the basis of enablement must be supported by some evidence or acceptable scientific reasoning as to why the particular claimed subject matter is not enabled. See *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971). Moreover, even though in an unpredictable art a single example may be insufficient to enable a generic claim, in the present instance there are numerous working examples, and the pending claims are directed to particular embodiments. The specification teaches the successful expression of at least 6 separate species. Moreover, none of the claims currently of record are truly generic in scope.

All that is required is that Applicants present evidence that the subject matter of the claims is reasonably reproducible, and that further practice of the invention would require only routine experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The *Wands* case is particularly relevant to the present determination in that *Wands* concerned the "how to use" requirement of section 112, and what was necessary to satisfy that requirement. In *Wands*, the PTO took the position that the

applicant failed to demonstrate that the disclosed biological processes could reproducibly result in a useful biological product (hybridomas) within the scope of the claims. In its decision overturning the PTO position, the Federal Circuit found that Wands' demonstration of success in four out of nine cell lines screened was sufficient to support a conclusion of enablement. The court emphasized that the need for some experimentation requiring, e.g., production of the biological material followed by routine screening, was not a basis for a finding of non-enablement. 8 U.S.P.Q.2d at 1406-7. Here, Applicants have demonstrated success in obtaining R1 expression in 6 out of 6 cases! Thus, there can be no question but that there is a reasonable expectation that the claimed genes will function in corn, and no evidence to the contrary.

For the foregoing reasons, the Examiner is respectfully requested to reconsider and withdraw the enablement objection to the specification.

X. Provisional Rejection of Claims 1-67 is Obvious Over Copending Application Serial No. 07/508,045

Next, the Action rejects all the pending claims provisionally as obvious over copending application Serial No. 07/508,045. The particular comments made in the Action with respect to this rejection are not entirely clear, as they appear to go to the question of enabling disclosure and patentable subject matter rather than the question of obviousness. Therefore, Applicants respectfully request clarification of the nature of the rejection in this regard.

Nevertheless, assuming that the Action's position is simply that the claims to the present application are not patentably distinct from the subject matter of the '045 application, Applicants will proceed on that basis. In response, while the '045 specification is recognized as fully enabling for the introduction and expression of any desired gene into corn, there is believed to be no basis for concluding that the introduction into corn of every gene is thereby rendered obvious. The Cohen-Boyer invention of gene cloning does not obviate every gene that the Kohler-Milstein technique of preparing hybridomas can clone. Similarly, the monoclonal antibody that has been prepared. Thus, the general techniques are known in the art for preparing transgenic corn do not obviate every gene that is claimed. The question of obviousness of the pending subject matter; Section 103 provides that "obviousness shall not be negated by the manner in which the invention was made." *In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993).

In the present instance, none of the presently claimed species are in any way specifically taught or anticipated by the '045 specification -- the '045 specification merely teaches the general technique of cloning genes in corn and gives examples of genes that are not obvious variants of the genes claimed in the present case. There is submitted to be no suggestion or motivation in the art for one of skill to substitute the genes of the present claims for those set forth in the '045 specification.

Lastly, Applicants point out that the PTO has consistently taken the position that the '045 specification is not generically enabling for fertile, transgenic corn, and that evidence of operability of one gene in corn does not support a conclusion that

other genes are so operable. This position appears to be contradicted by the position taken here under obviousness-type double patenting in that the PTO has taken the position that '045 is not broadly enabling. See, e.g., *Dewey & Almy Chem. Co. v. Mimex Co.*, 52 U.S.P.Q. 138 (2d Cir 194); *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979) ("References relied upon to support a rejection under 35 U.S.C. 103 must provide an enabling disclosure, *i.e.*, they must place the claimed invention in the possession of the public An invention is not 'possessed' absent some known or obvious way to make it . . ."). Thus, if the present rejection is maintained, Applicants request clarification as to how the parent specification can be considered non-enabling by the PTO, yet be relied upon for the present obviousness rejection.

XI. Rejection of Claims 1, 2, 5, 9-16, 43-46 and 61 Under 35 U.S.C. § 103

Next, Claims 1, 2, 5, 9-16, 43-46 and 61 are said to be obvious over the *Spencer et al.* FASEB Poster in view of *Phillips et al.*

In response, Applicants first point out that of the rejected claims, only claim 61 remains pending. It is respectfully submitted that the subject matter of claim 61 is in no way taught or suggested by *Spencer et al.* in view of *Phillips et al.* Claim 61 is directed to certain particular tissue specific or inducible promoters -- an α -tubulin promoter, actin promoter, *ocs* promoter, sn ABA-inducible promoter or a turgor-inducible promoter -- in fertile, transgenic corn. However, neither reference teaches nor suggests tissue specific promoters that are used to control transgene expression in fertile, transgenic corn. *Spencer* discloses only the use of a 35S promoter and an

Adh1 promoter. However, none of the particular claimed promoters are disclosed or suggested in either reference relied upon by the Examiner.

Applicants are also firmly of the opinion that the Spencer et al. poster is in no way enabling for the subject matter of the invention. Spencer discloses merely the preparation of transformed embryogenic or non-embryogenic maize cells. However, there is no teaching or suggestion from Spencer that plants regenerated from these cells were fertile -- fertility is a key aspect of the present invention in that early attempts to obtain transgenic corn resulted in only the realization of sterile plants. The plants that are mentioned in passing by Spencer as having been prepared are not shown to be fertile. Therefore, it is submitted that those of skill in the art would not conclude that fertility had been achieved by Spencer, in that Spencer in no way teaches or suggests that the plants were fertile.

XII. Rejection of Claims 1-67 Under 35 U.S.C. § 103

Next, all the claims to reject as obvious over Goldman *et al.* in view of what the Examiner states as "Applicants' acknowledged state of the prior art." The Action takes the position that Goldman *et al.* discloses the preparation of fertile transgenic corn.

In response, it is respectfully submitted that the Goldman *et al.* patent does not claim, and fails to enable, fertile, transgenic corn plants as defined by the pending claims, and fails to disclose an operable method for obtaining fertile transgenic corn plants. Importantly, in the Goldman *et al.* prosecution itself, the PTO has consistently

and steadfastly maintained that it does not enable fertile, transgenic corn plants. Thus, in light of the PTO's position in the Goldman prosecution, it is untenable for the Examiner in the present case to maintain a position of obviousness over Goldman *et al.*.

Goldman *et al.* purports to disclose methods for the production of fertile, transgenic maize plants using *A. tumefaciens*. However, Example III of Goldman *et al.* is entirely prophetic in its purported disclosure of fertile plants, and Example XI purports to disclose only the production of octopine in progeny, a notoriously inappropriate marker for transgenic expression in maize due to unacceptably high background levels in non-transformed plants.

Maize is not a natural host for *Agrobacterium*, not because it is a monocot, but because it does not exhibit a wound response as do species susceptible to *Agrobacterium* infection. (See, Potrykus, *Biotechnology* 7:535-542). Cereals in general do not exhibit the wound response that is necessary for successful integrative *Agrobacterium* transformation. Instead, as explained by Potrykus, cereal cells die when wounded, whereas most dicots and some monocots species respond to wounding by dedifferentiation and cell proliferation in adjacent cells. Moreover, that tissue competent to receive *Agrobacterium* DNA, meristematic cells, is probably not competent for integrative transformation (Potrykus, 1990). Thus, a cereal cell which has been infected with *Agrobacterium* is fated to die.

While it is true that viral DNA can be delivered to maize via *Agrobacterium tumefaciens* in a process termed "agroinfection" (Boulton *et al.*, *Plant Molecular*

Biology 12:31-40, 1989, copy enclosed), successful virus infection is based upon the ability of the virus to move from cell to cell and spread to sites away from the wound inoculation site, i.e., those cells fated to die in response to wounding. If the DNA were integrated into the host genome of the wounded recipient cell as purported by Goldman *et al.*, a successful viral infection would not occur because the virus would be unable to move the healthy proliferating cells away from the wound inoculation site.

The fact that under the conditions described by Goldmann *Agrobacterium* is incapable of transmitting DNA in transmissible manner is further evidenced by the enclosed article of Shen et al. (*The Plant Journal*, 5:227-236, 1994). These authors inoculate maize in the same manner as Goldman and Graves and demonstrate GUS expression in leaves that were preformed at the time of inoculation (leaves 1-5), but no expression in later formed leaves (see left column, page 230, and right column, third paragraph, page 233). Although Shen and Hohn use this observation to demonstrate that a virus is not moving in the plant, it also demonstrates that the cells that would later form the germ line of the plant were not inoculated. These observations by Shen and Hohn are consistent with Goldman and Graves' observation of putative expression of opine compounds in the first two weeks after inoculation with *Agrobacterium*, but are strong evidence that this method will not produce fertile transgenic progeny.

The inapplicability of the Goldman *et al.* patent to the present invention is further evidenced by the fact that Goldman *et al.* discloses inoculation of maize

seedlings with *Agrobacterium* strain CA19 (a derivative of strain Ach5) and purports to produce fertile transformed plants in Example XI using this strain. However, even agroinfection of maize with MSV using *Agrobacterium* as a vector is highly dependent upon the strain of bacteria used. In particular, Boulton *et al.* (supra) demonstrated that whereas it was possible to achieve agroinfection of maize plants with MSV using nopaline producing strains of *Agrobacterium* such as C58, it was not possible to do so using nopaline producing strains such as Ach5 and others (see Table 1, Boulton *et al.*, 1989). Thus, it is highly improbable that Goldman could have achieved even non-integrative agroinfection with Ach5-derived strains.

Of particular importance is the fact that Goldman *et al.* relies only upon the detection of octopine to verify that transformation has occurred. These assays detect the conversion of arginine to an opine compound, and are notoriously unreliable as proof of the presence of T-DNA. Christou *et al.* (Plant Physiology 82:218-221, 1986, copy enclosed) demonstrated that normal callus and plant tissue of several species of plants, including maize (page 220) are capable of converting arginine to nopaline in the absence of T-DNA! Thus, the presence of enzyme activities that will convert arginine to opine compounds is to be expected in maize cells that do not contain T-DNA and hence, there is no definitive evidence that the plants disclosed by Goldman *et al.* were transformed.

Lastly, it is pointed out that the PTO has consistently taken the position on the Goldman *et al.* record, that Goldman *et al.* is NOT enabling for the preparation of transgenic corn *per se*, and, at best, merely describes one technique for transferring

T-DNA. In this regard, Applicants direct the present Examiner's attention to the file history of USSN 06/880,271, a now-abandoned parent of Goldman *et al.*, in which the Applicants sought allowance of claims directed to transformed corn plants *per se*.

For example, in an Office Action dated 5/30/89 (copy enclosed), the PTO stated that a claim directed generally to transgenic corn plants were rejected under 35 U.S.C. § 112, first paragraph, stating that:

The specification only demonstrates the expression of heterologous genes, namely opine synthases, in seedling tissue or plant parts directly derived from growing the transformed seedling. No demonstration of stable gene integration or sexual transmission of the exogenous gene, other than prophetic examples, is shown. Given the recalcitrance of monocots to Agrobacterium transformation, as discussed by Applicants, and the possibility of transient opine synthase expression by non-integrative genes, as discussed by Hernalsteens *et al.* (see, e.g., page 3040, column 2, second paragraph), undue experimentation would be required by one of ordinary skill in the art to obtain stable gene integration or sexual transmission of the exogenous gene as claimed.

In response, the Applicants failed to present any additional data *per se* on the record in support of a conclusion that stable integration had been achieved, merely pointing to new matter added as what is now Example XI of the Goldman *et al.* patent. However, this example merely relates to the purported demonstration of opine synthesis, already found by the Examiner to be an insufficient test for stable gene integration.

In the next Office Action (OA of 3/8/90; copy enclosed), the rejection was maintained, with the Examiner making the following relevant comments of record:

Applicants urge that rejection of the claims as being non-enabled for transformed plants obtained by sexual reproduction is improper, given the demonstration of opine synthase expression in cells directly derived from transformed meristematic cells. The Examiner maintains that opine synthase

is an insufficient test for stable gene integration (see, e.g., Christou *et al.*, which discloses opine production by untransformed cells). (emphasis supplied)

The application became abandoned based upon the Applicants failure to respond to the 3/8/90 Office Action. It is submitted that the Applicants abandonment of the general transgenic plant claims in light of rejections such as the foregoing is strong evidence that Goldman *et al.* is not enabling for the production of fertile, transgenic corn plants. Moreover, it is submitted that the current PTO position with respect to the lack of enablement of the Goldman *et al.* disclosure in this regard is set forth in the two aforementioned Office Actions, and it would be surprising for the present Examiner to take a contrary position without further proof being submitted by Goldman *et al.*

For the foregoing reasons, the Examiner is requested to reconsider and withdraw the rejection based upon Goldman *et al.*

**XIII. Rejection of Claims 7, 20, 73(?),
1-4 and 9 Under 35 U.S.C. § 103**

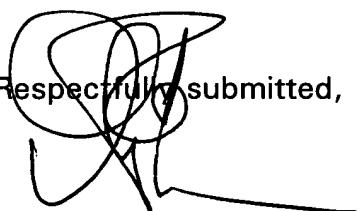
Lastly, the Examiner has rejected various of the claims over various references on the basis of 35 U.S.C. § 103. These rejections are generally based on the Examiner's positions that the claims do not *per se* distinguish over naturally occurring plants that exhibit certain traits. While Applicants continue to be of the firm opinion that the claims do, in fact, distinguish over naturally occurring plants, Applicants point out that none of the claims rejected by the Examiner on this basis are currently pending. (While it is true that claims 2-4 are currently pending, the dependency of

these claims has been altered and they are now depending from claims others than claim 1.) Additionally, the Examiner mentions claim 73, but Applicants point out that there is no such claim pending in this case.

XIV. Conclusion

It is respectfully submitted that the present response is a complete response to the outstanding Action. If the Examiner has any questions, comments or suggestions, a telephone call to the undersigned Applicants' representative is respectfully requested.

Respectfully submitted,


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